CDER New Drug Review: 2014 Update

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FDA/CMS Summit
December 11, 2014
Slides posted at:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm074833.htm

Housekeeping

- Data and analyses presented on the following slides are thought to be accurate. In order to provide the most up-to-date information the analyses have not undergone the same thorough quality control as is performed for official FDA reports
- Many staff in CDER provided data, analyses, and PowerPoint expertise for this talk; their work behind the scenes makes me look good each year. Special thanks and acknowledgement to:
  - The Performance Analysis Staff in CDER's Office of Program and Strategic Analysis
  - Mike Lanthier in the Office of the Commissioner
- Pay attention to fiscal year (FY) or calendar year (CY) on data presentations

Themes in new drug review for 2014

- The NME "Program" is running smoothly
- Breakthroughs, breakthroughs, breakthroughs!!!
  - (and a lot of breakthrough wannabes)
- Strong year for NME approvals but filings remain flat
- First-cycle approval rates remain high
- Best year ever for rare disease NME approvals
- US continues to lead the world in first approval on NMEs
- Much-needed renewed activity in antibacterial NMEs
- First biosimilar BLAs under review
- Despite successes, challenges remain
  - Increasing workload as new programs/expectations are added
  - Continuing resolution and travel restrictions
  - Recruitment and retention of staff

Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
  - IND activity, NME submissions, and NME approvals
- Implementation of PDUFA V/FDASIA programs
  - "Program" for NME review
  - Breakthrough Therapy Designation Program
  - Benefit/risk framework

What about PDUFA Goals?

- FDA continues to meet or exceed nearly all PDUFA goals for application review
- We are working to implement the enhancements agreed to under PDUFA V and the new FDASIA programs as resources and competing priorities allow
  - Funding situation somewhat improved from 2013, but still under CR
  - Small net growth in onboard staffing in OND
    - 916 FTEs on board at start of PDUFA V/FDASIA (FY13)
    - 975 FTEs on board at start of FY15
    - Still well below FTE ceiling (1058 FTEs) and staffing requirements to meet increasing workload; e.g., Breakthrough, biosimilars, PFDD, GAIN, B/R framework, GDUFA, priority review vouchers, etc……..
  - Federal hiring system, pay freezes, pay caps, outdated pay system, etc. adversely impact on ability to recruit and retain necessary staff

What About New Drug Approvals?

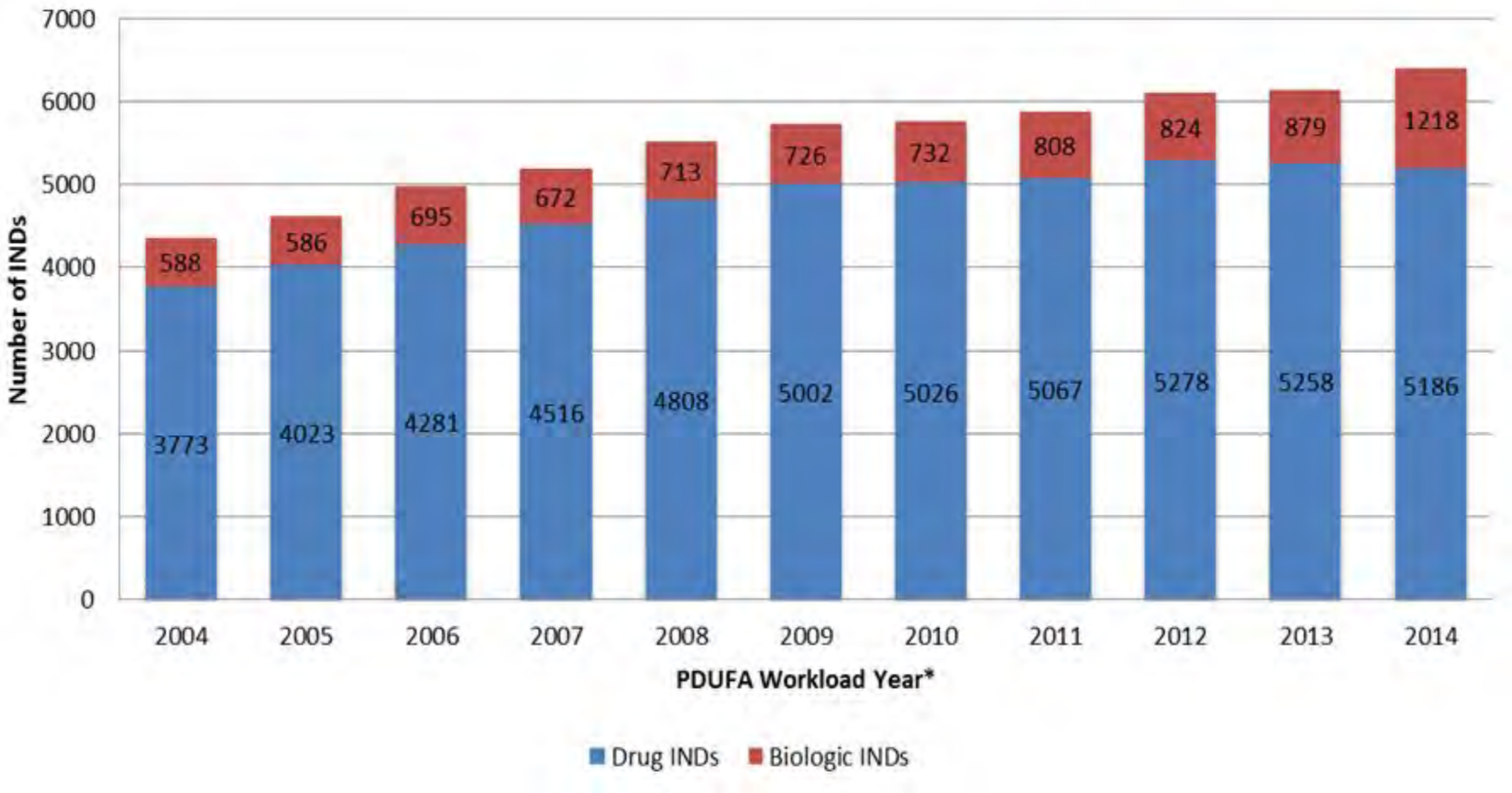
- The commercial IND pipeline of new drugs under development remains strong; growth driven by biologics
- Through December 3, 2014, CDER has received 35 NME applications in CY2014
  - Some are still within the 60-day filing window, subject to RTF
  - 10-year average NME filings = 34
- To date in CY2014 CDER has approved 35 NMEs
  - 10-year average NME approvals = 26
  - 3 NMEs approved in Jan/Feb 2014 "shifted" to CY2014 by Program
- 7 Breakthrough NMEs approved to date in CY2014
- 15 Orphan NMEs approved to date in CY2014
  - Highest total since passage or Orphan Drug Act
- First cycle approval rates remain high, median time to approval up slightly due to Program

CDER Review Performance

	FY 2013		FY 2014	
Submission Type	Number Filed	Performance (Current)	Number Filed†	Performance (Potential)**
Priority NME NDAs/original BLAs	17	100%	25	100%
Standard NME NDAs/original BLAs	29	93%	15	100%
Priority non-NME NDAs*	8	88%	9	89%
Standard non-NME NDAs*	76	97%	71	100%
Class 1 NDA/BLA Resubmissions	9	100%	7	100%
Class 2 NDA/BLA Resubmissions	36	97%	31	100%
Priority Efficacy Supplements	28	96%	37	100%
Standard Efficacy Supplements	108	92%	131	99%
Class 1 Efficacy Resubmissions	1	100%	7	100%
Class 2 Efficacy Resubmissions	7	86%	8	88%
Prior Approval Mfg Supplements	637	90%	555	95%
CBE Mfg Supplements	1147	93%	1009	97%

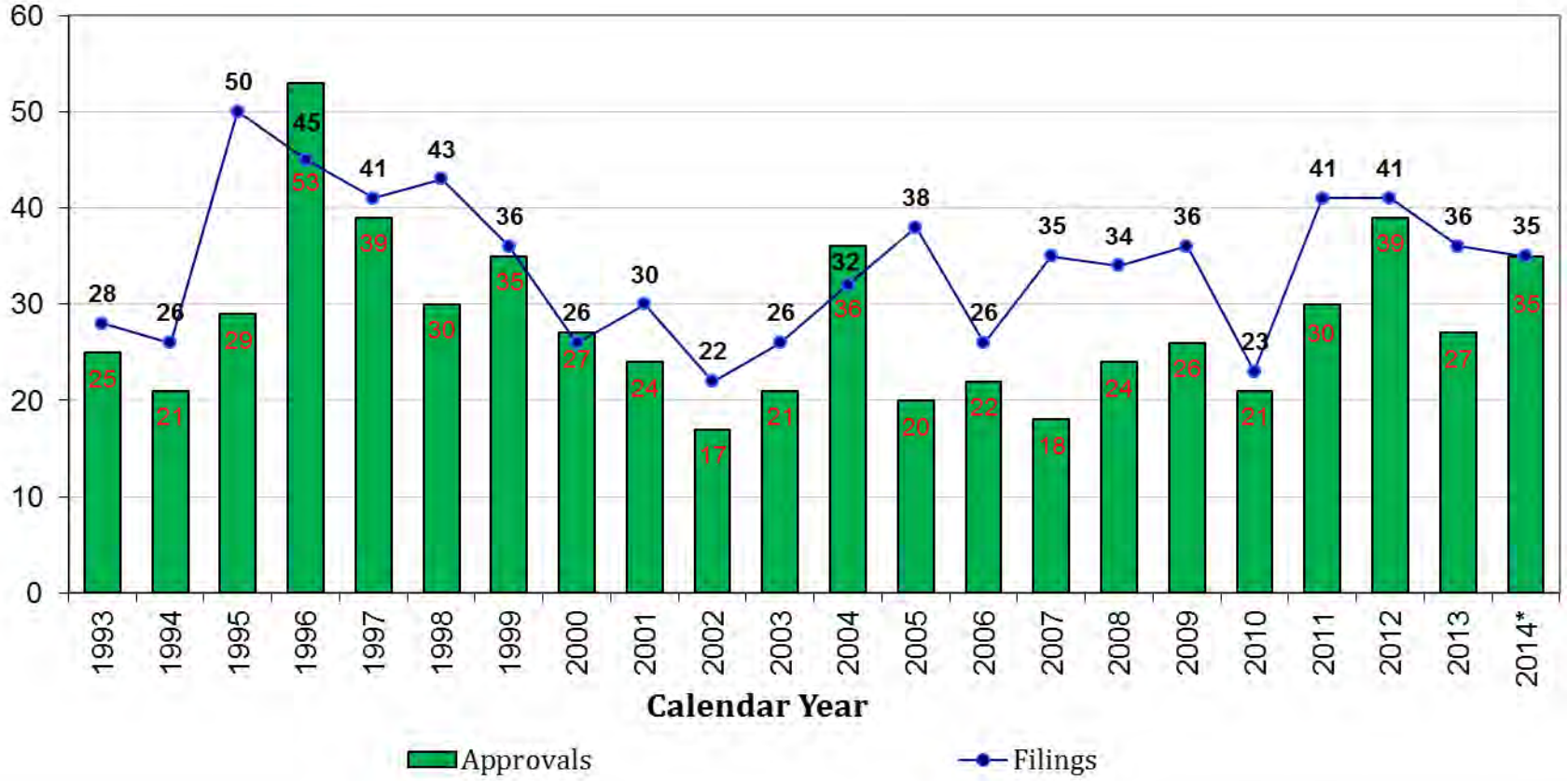
Data as of 9/30/2014
*Beginning in FY 2013, the new tracked metrics are non-NME Priority and non-NME Standard NDAs.
† Includes submissions pending filing.
**Potential Performance refers to the level of performance that could potentially be achieved if all the actions currently pending are reviewed within their required goal date. Submissions with unknown review schedules are excluded.

Commercial INDs With Activity Based On PDUFA Workload Adjuster Data



Data represents 12 month period of July 1st - June 30th

CDER NME NDAs/BLAs† Filings and Approvals



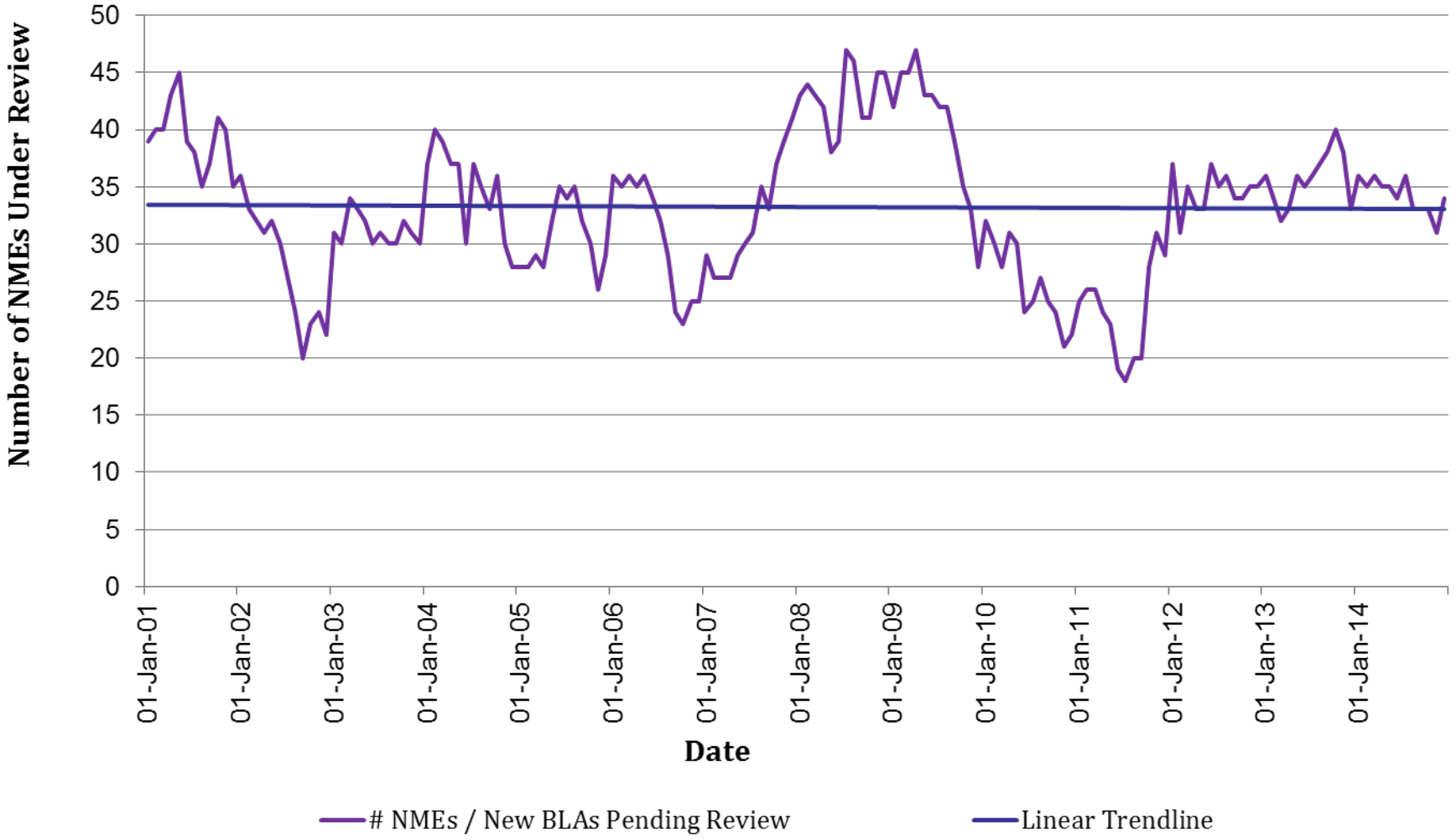
Data as of 12/3/2014

† Multiple applications pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for CY14 filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

*Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.

Number of NMEs Concurrently Under Review



* Data as of 11/30/2014.

Snapshot of CY 2014
NME NDAs/BLAs† Drug Approvals (1/2)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Orphan Drug	Breakthrough Therapy	QIDP
FARXIGA									
HETLIOZ									
VIMIZIM									
NORTHERA									
MYALEPT									
NEURACEQ									
IMPAVIDO									
OTEZLA									
TANZEUM									
CYRAMZA									
SYLVANT									
ZYKADIA									
ZONTIVITY									
ENTYVIO									
DALVANCE									
JUBLIA									
SIVEXTRO									

Data as of 12/3/2014

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

*A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

QIDP - Qualified Infectious Disease Product

Snapshot of CY 2014
NME NDAs/BLAs† Drug Approvals (2/2)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Orphan Drug	Breakthrough Therapy	QIDP
BELEODAQ									
KERYDIN									
ZYDELIG**									
STRIVERDI RESPIMAT									
JARDIANCE									
ORBACTIV ***									
BELSOMRA									
PLEGRIDY									
CERDELGA									
KEYTRUDA									
MOVANTIK									
TRULICITY									
LUMASON									
AKYNZEO									
HARVONI									
ESBRIET									
OFEV									
BLINCYTO									

Data as of 12/3/2014

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

** ZYDELIG was submitted with two indications of which one of the indications was granted a Breakthrough Therapy , Fast Track and Priority Review.

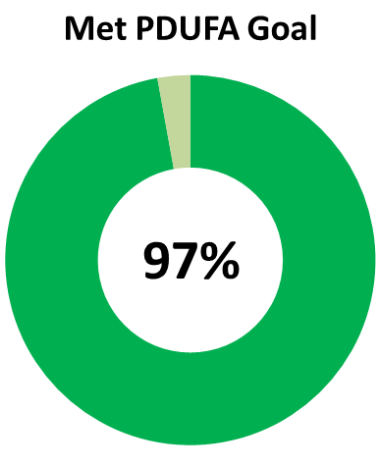
*** ORBACTIV was originally submitted in 2008 and received a complete response. The original applicant was purchased by another company and ORBACTIV was resubmitted under a new NDA with new clinical developments and was approved.

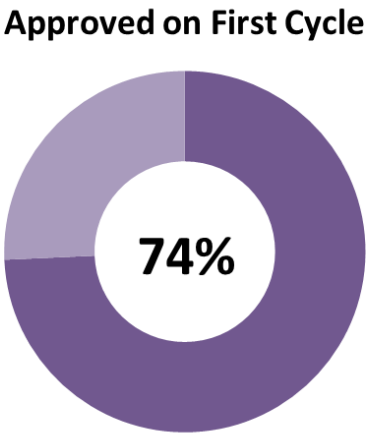
QIDP - Qualified Infectious Disease Product

In CY 2014, CDER Continued To Ensure The Efficiency Of First Cycle Review

- All but one of the novel drugs approved to date in CY14 met their PDUFA goal dates for the approval review cycle

- Almost three-quarters (74%) of the novel drugs, approved to date in CY14, were approved in the first review cycle

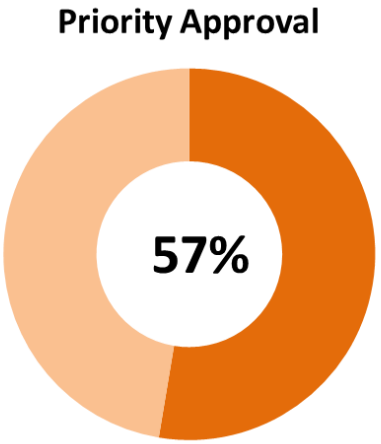


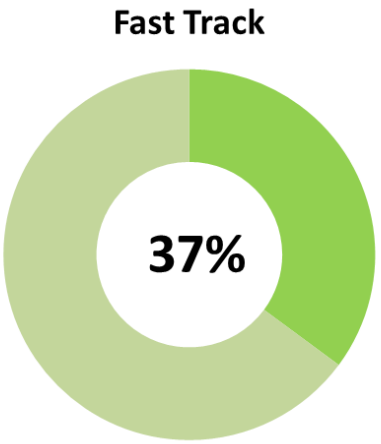


CDER Ensures That Novel Drugs Receive Expedited Review

- More than half (57%) of the novel drugs approved to date in CY14 were approved under Priority Review

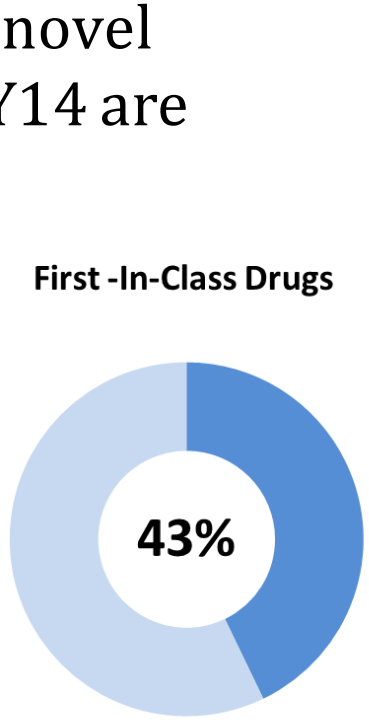
- More than one-third (37%) of novel drugs approved to date in CY14 received Fast Track designation

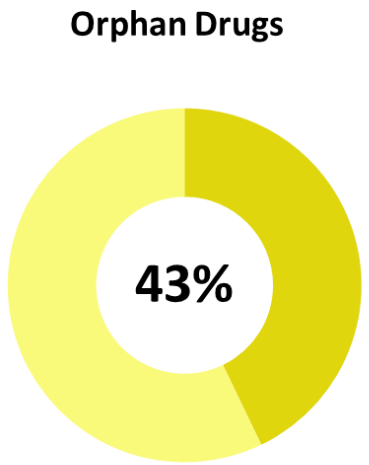


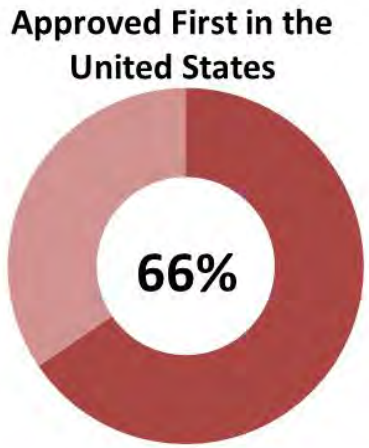


2014 Continues A Strong Track Record For Drug Innovation

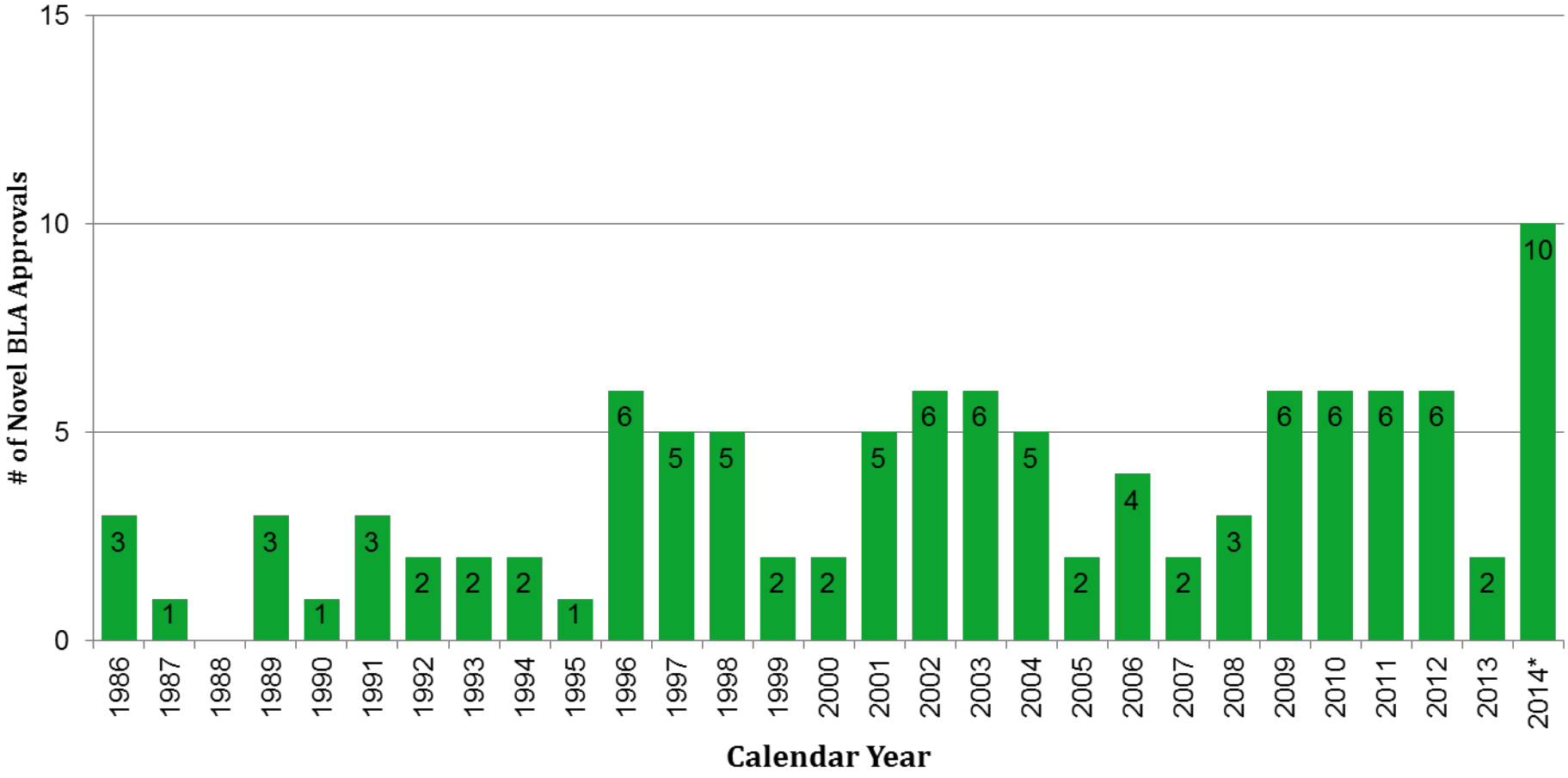
- Four out of every ten (43%) novel drugs approved to date in CY14 are for rare diseases
- Four out of every ten (43%) of novel drugs approved to date in CY14 are the first in their class
- Two-thirds (66%) of novel drugs approved to date in CY14 were first approved in the U.S.





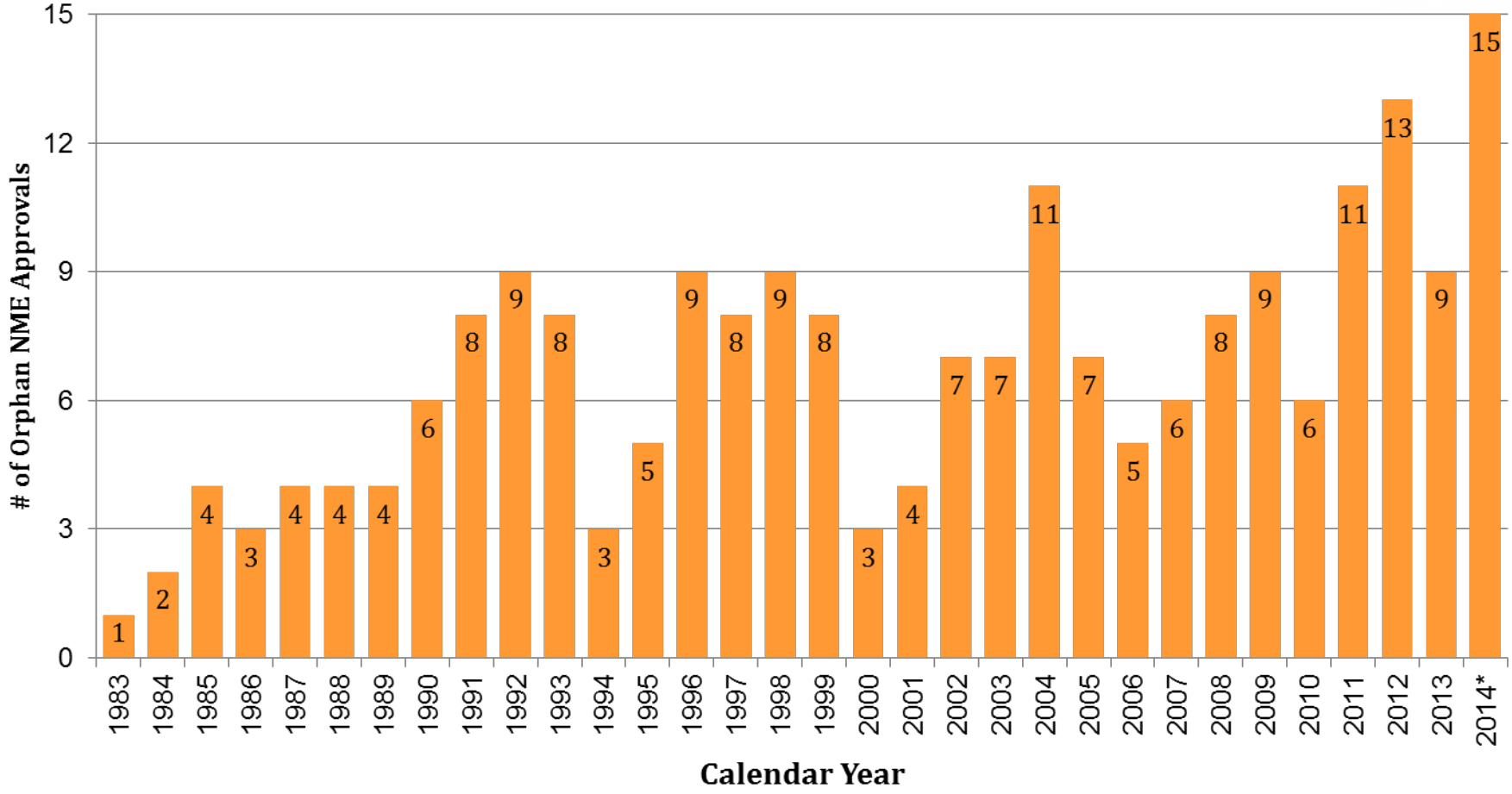


CDER Therapeutic New Biologic Approvals



*Data as of 12/3/2014. Includes novel therapeutic BLAs regulated by CDER, including those approved by CBER prior to the CDER/CBER consolidation which occurred in 2004.

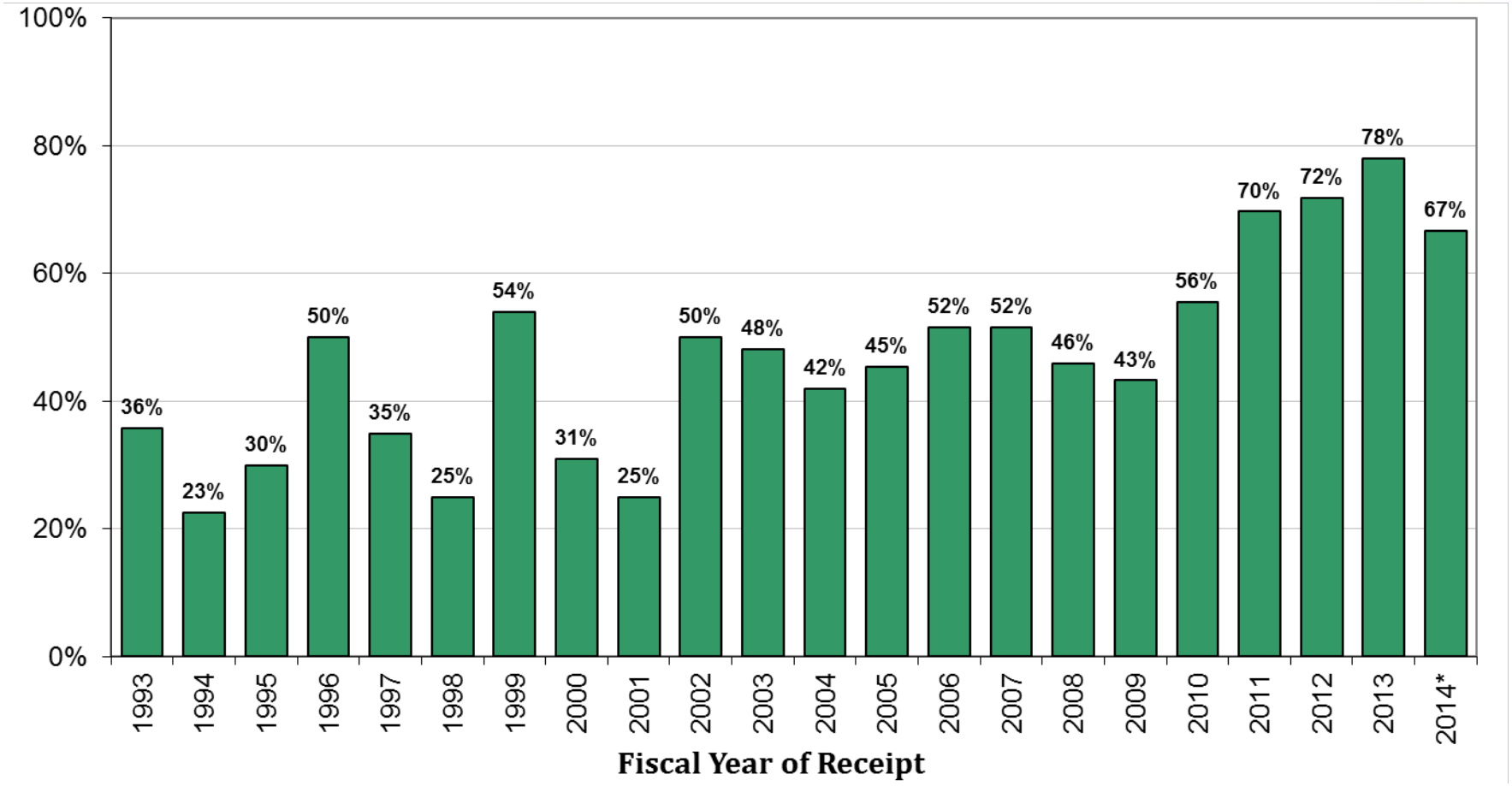
CDER Orphan NME and New Biologic Approvals



Data as of 12/3/2014

*2014: Most rare disease NME approvals since the 1983 Orphan Drug Act.

CDER NME NDAs/BLAs†
First Action Approval Rate



Data as of 12/3/2014

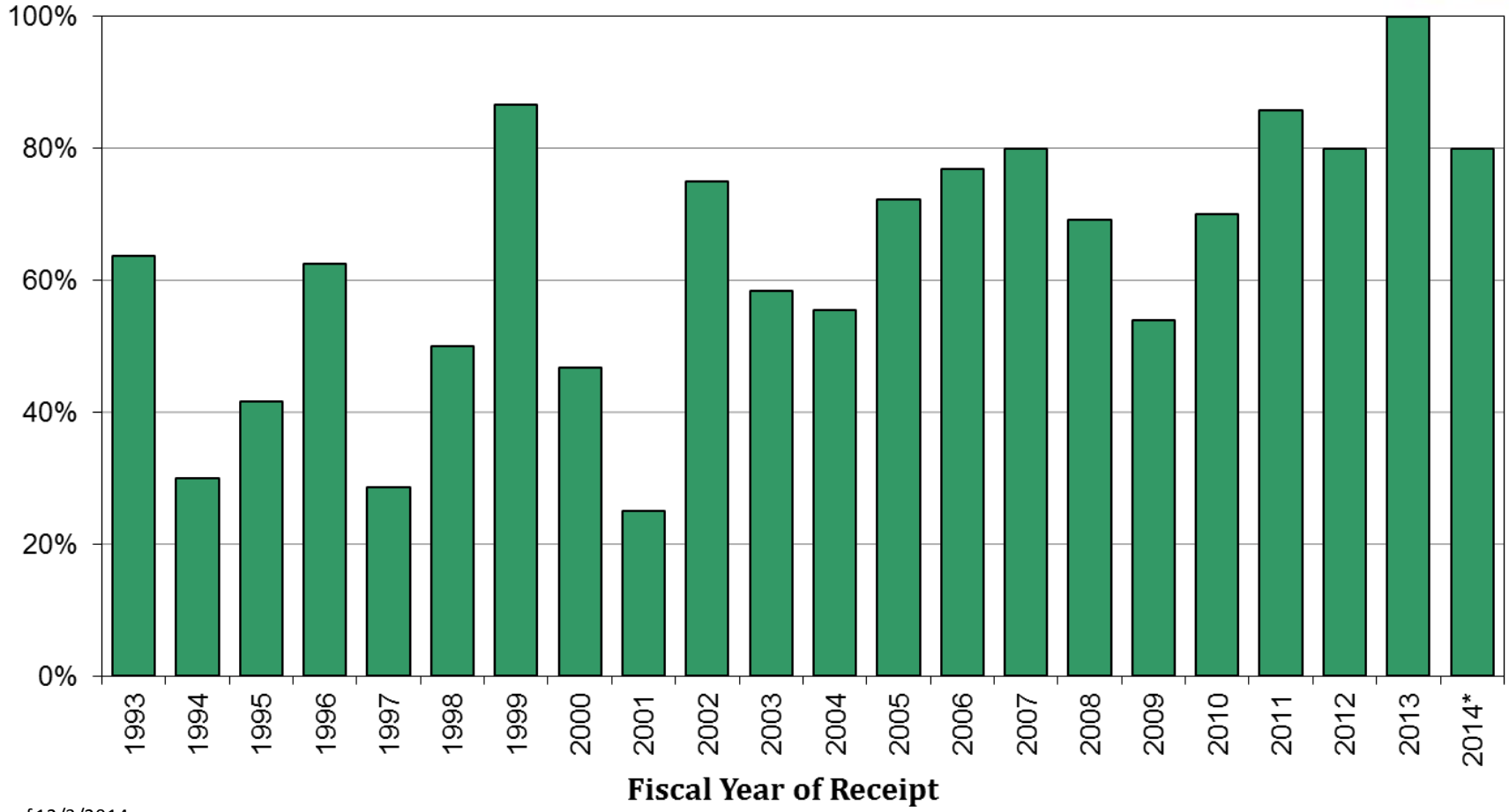
† Multiple applications pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

Percentages exclude pending applications from the denominator.

* FY 14 Cohort has 24 pending applications.

CDER First Action Approval Rates For Priority NME NDAs/BLAs†



Data as of 12/3/2014

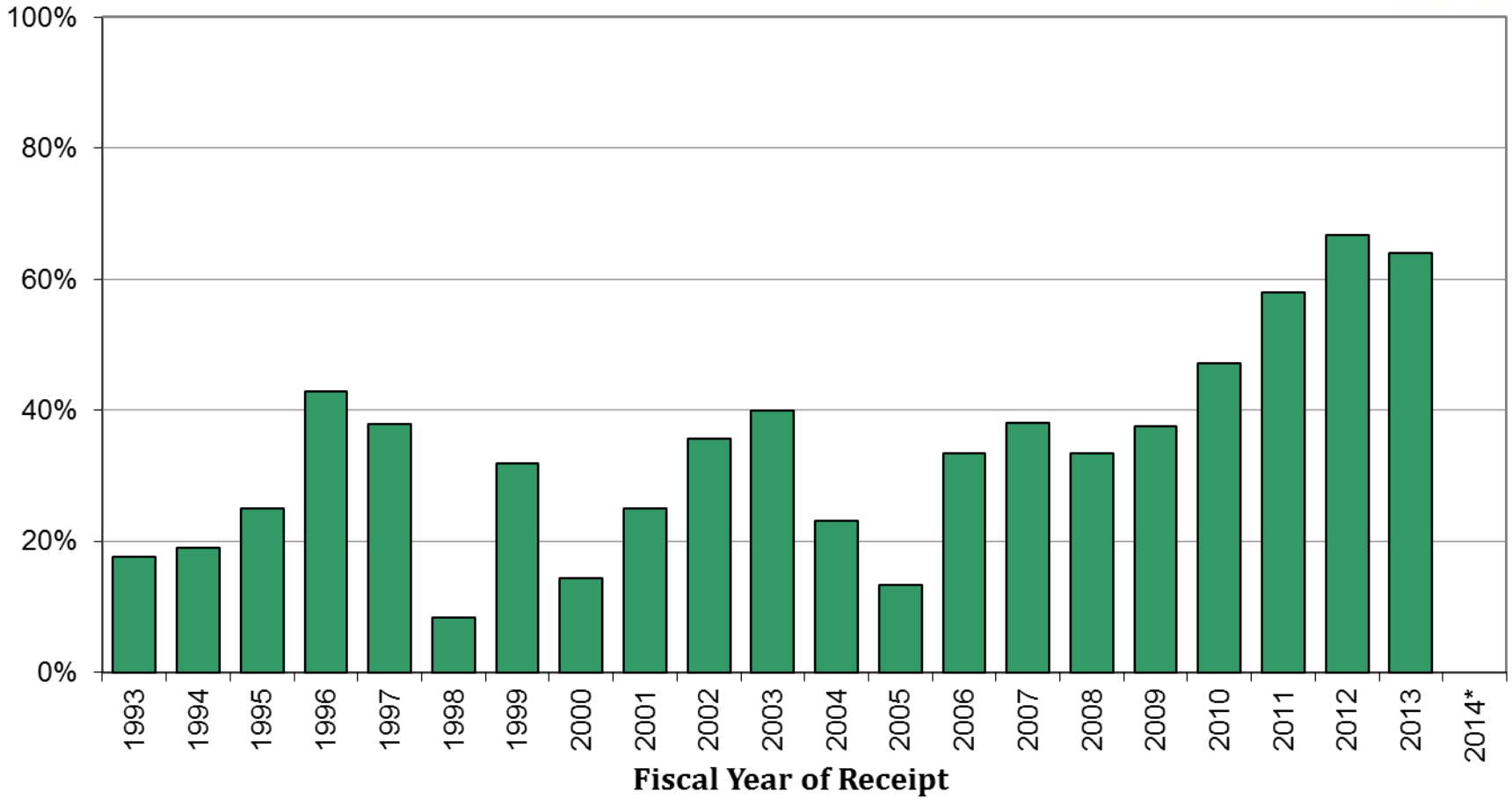
† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

Percentages exclude pending applications from the denominator .

* FY 14 Cohort has 12 pending priority applications.

CDER First Action Approval Rates For Standard NME NDAs/BLAs†



Data as of 12/3/2014

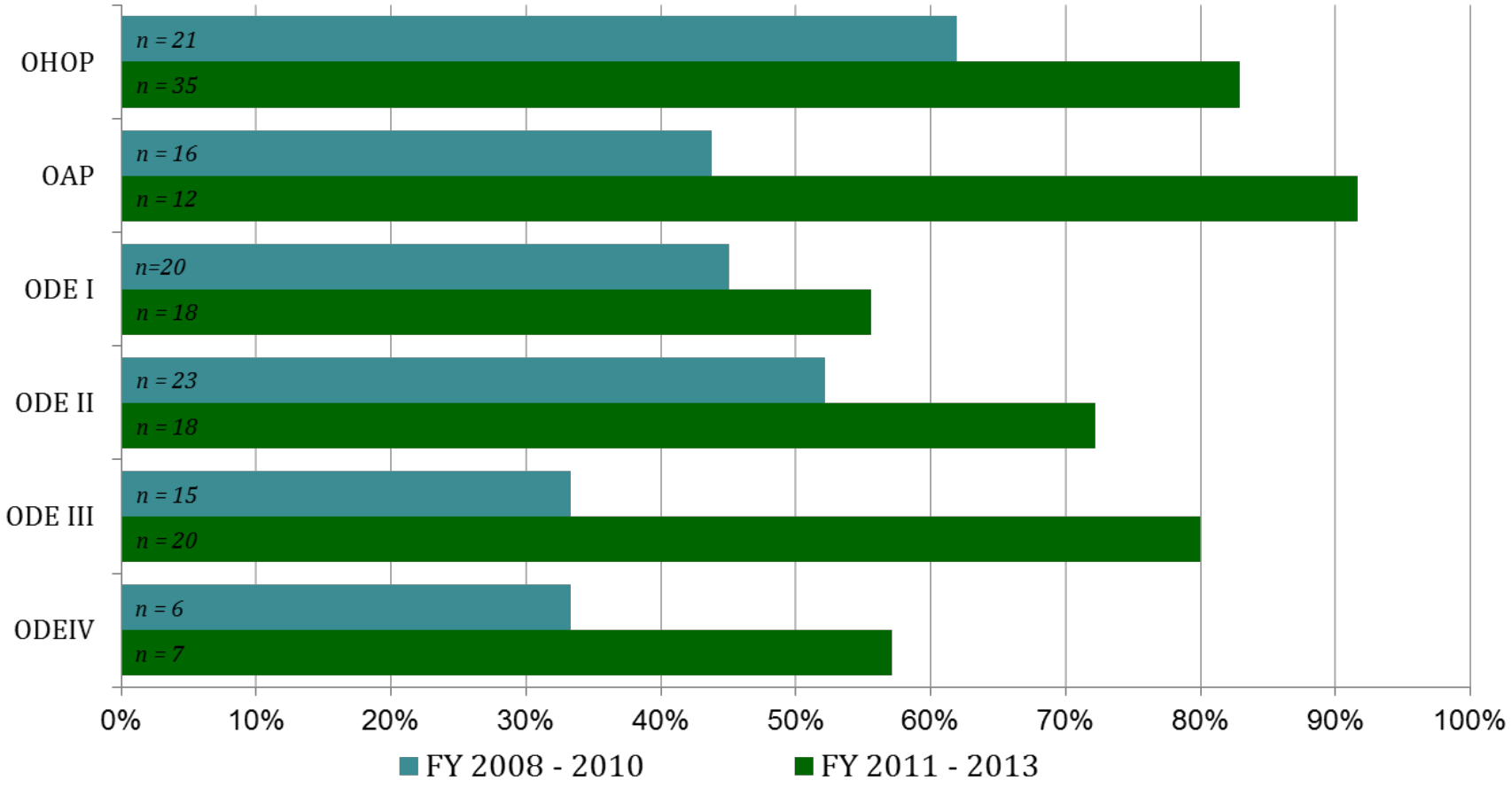
† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

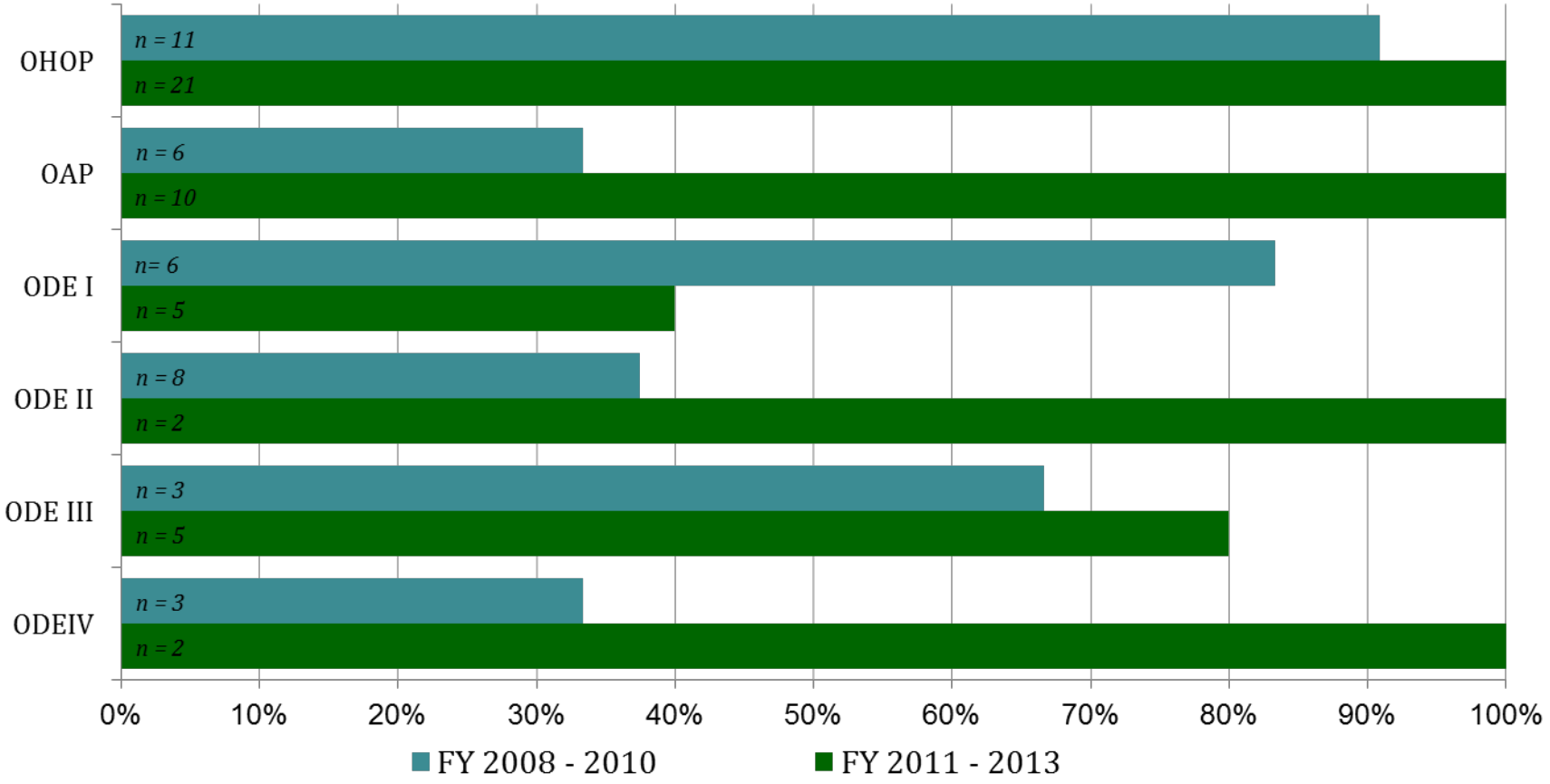
Percentages exclude pending applications from the denominator.

* FY 14 Cohort has 12 pending standard applications. There are no FY14 standard approvals as of 12/3/2014. One application received a CR and one was WD before action.

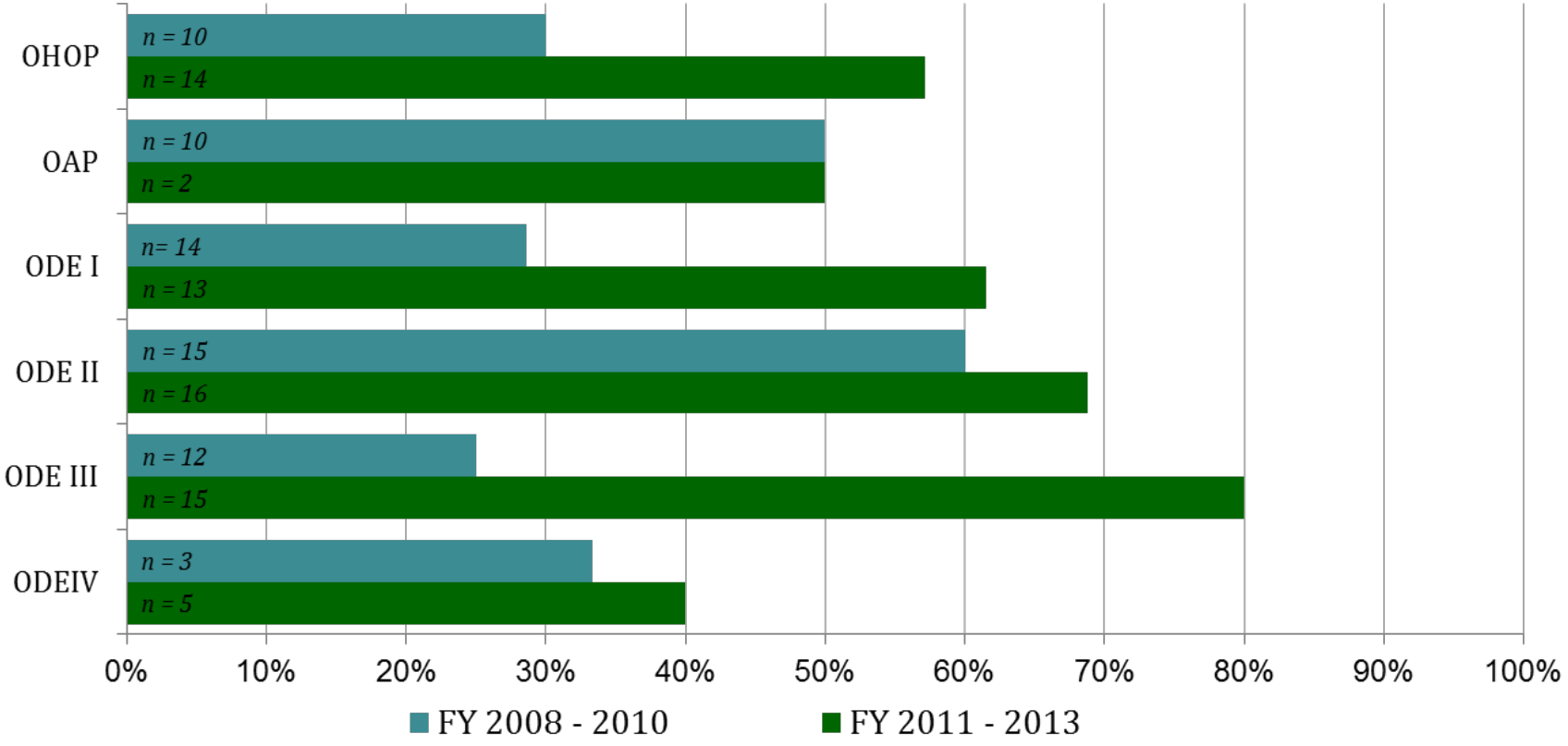
NME/NBE First Cycle Approval Rates FY 2008-2010 vs. FY 2011-2013



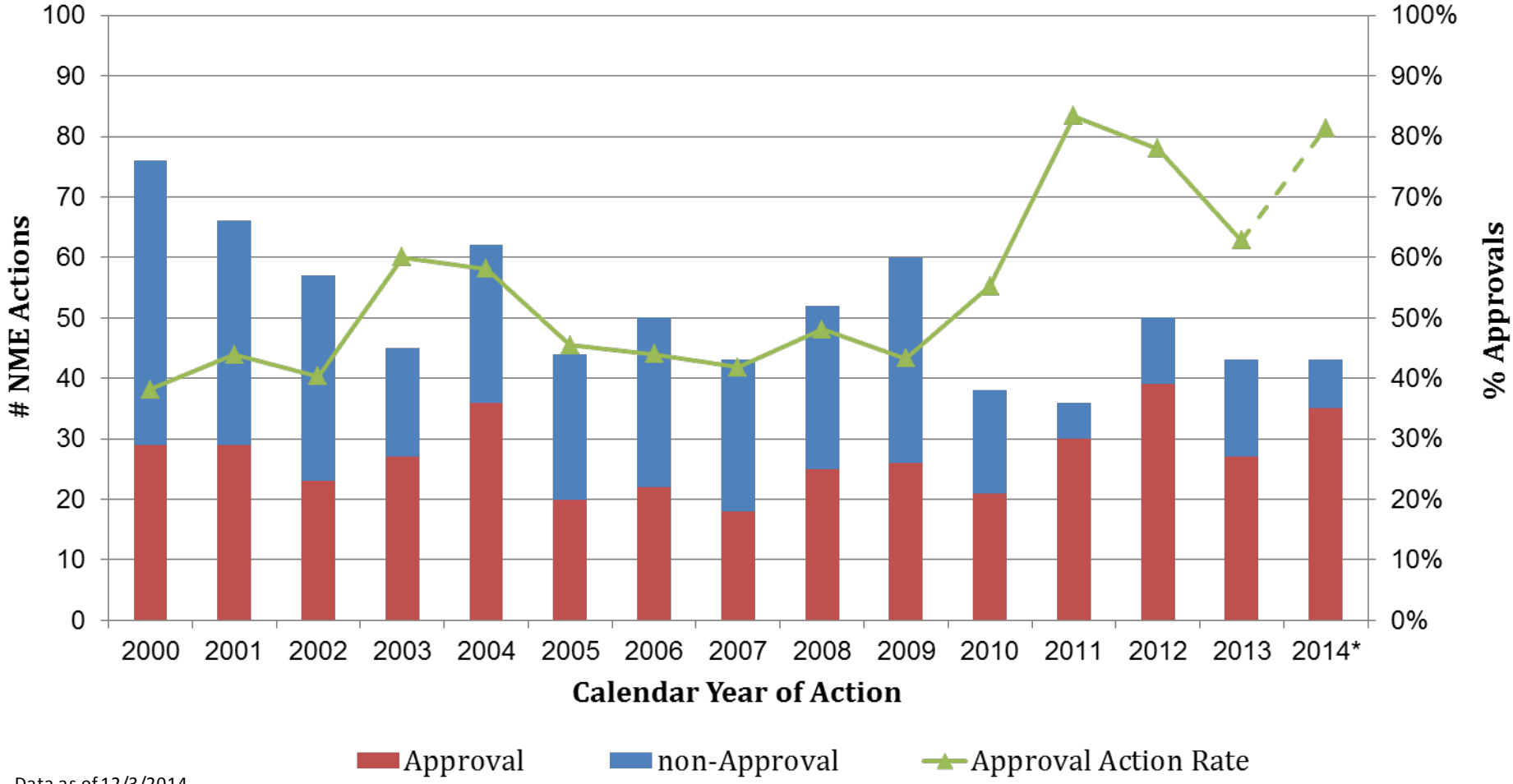
Priority NME/NBE First Cycle Approval Rates FY 2008-2010 vs. FY 2011-2013



Standard NME/NBE First Cycle Approval Rates FY 2008-2010 vs. FY 2011-2013



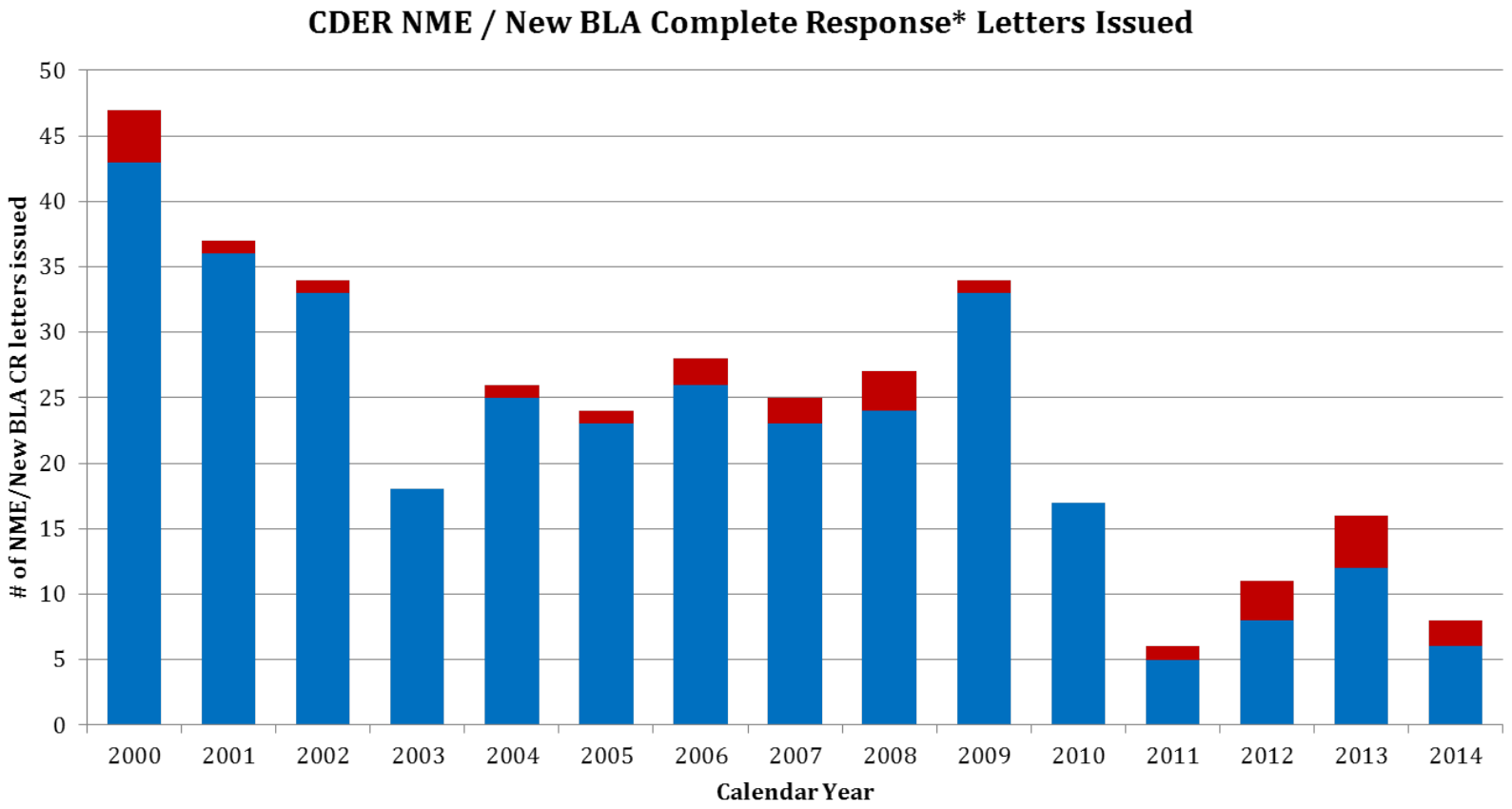
NME Actions and Approvals



Data as of 12/3/2014

Includes discrete actions on a given date for an active ingredient which, if approved, would constitute a new molecular entity. Actions for original submissions and resubmissions as well as actions for new BLAs are included. Multiple actions which occur on the same date for multiple dosage forms or indications are counted as a single regulatory action.

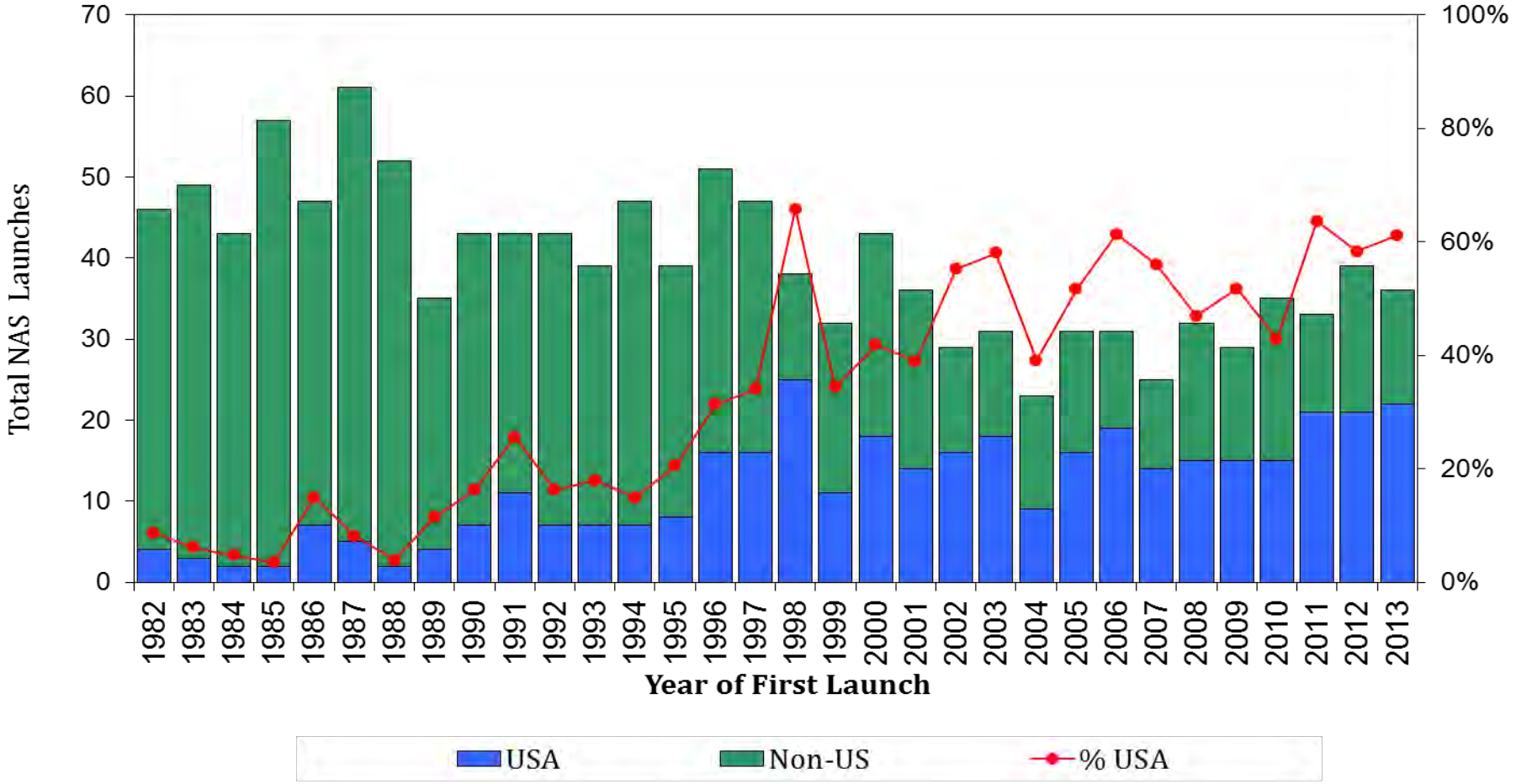
CDER NME/New BLA Complete Response* Letters Issued



Data as of 12/3/2014

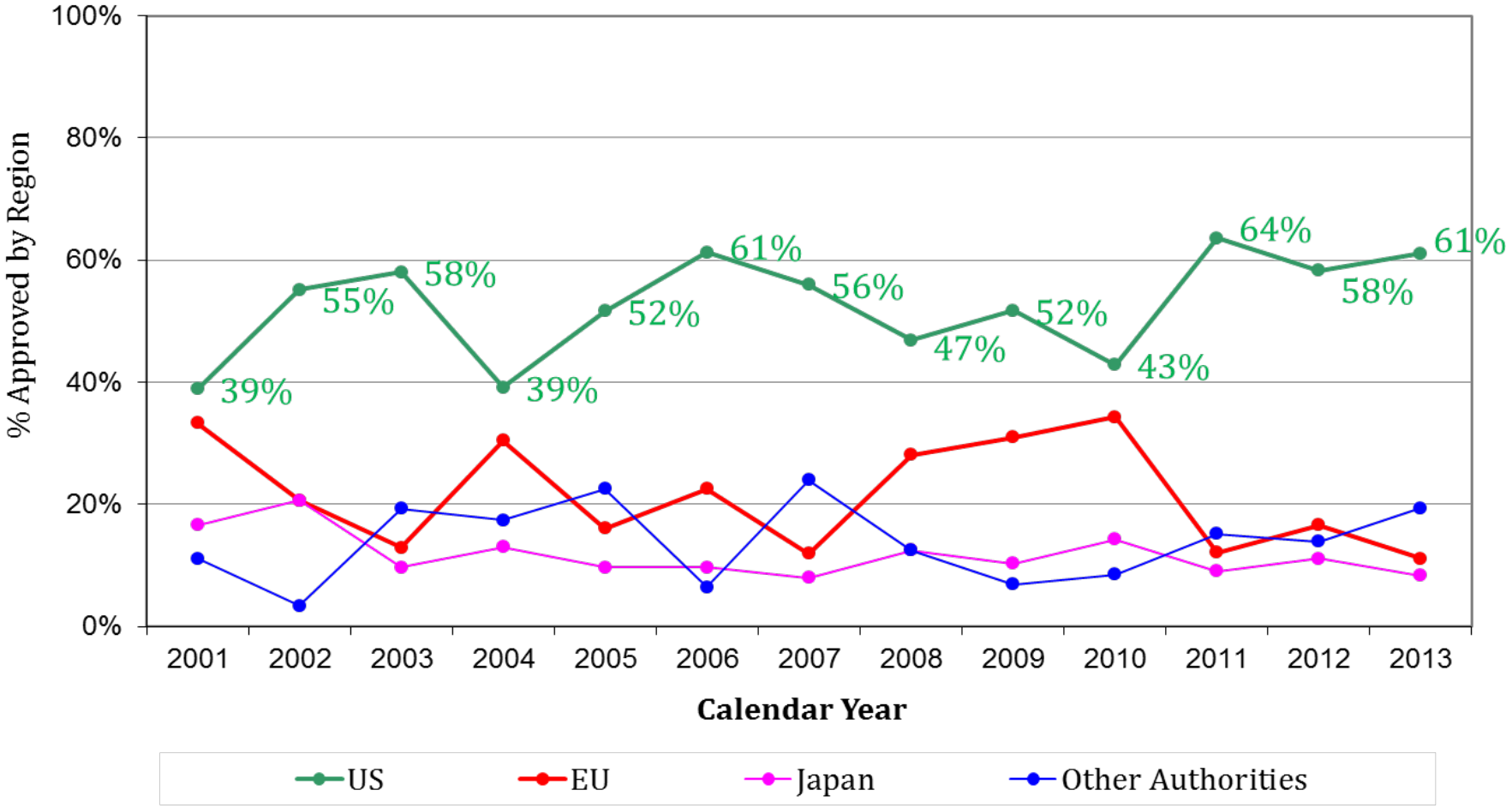
* Complete Response letter figures include "approvable" and "not approvable" letters issued for NDA actions prior to August 11, 2008, the date the Complete Response Letter rule was finalized. Counts do ***not*** include NDAs withdrawn by a sponsor prior to FDA action.

USA Share of New Active Substances Launched on World Market



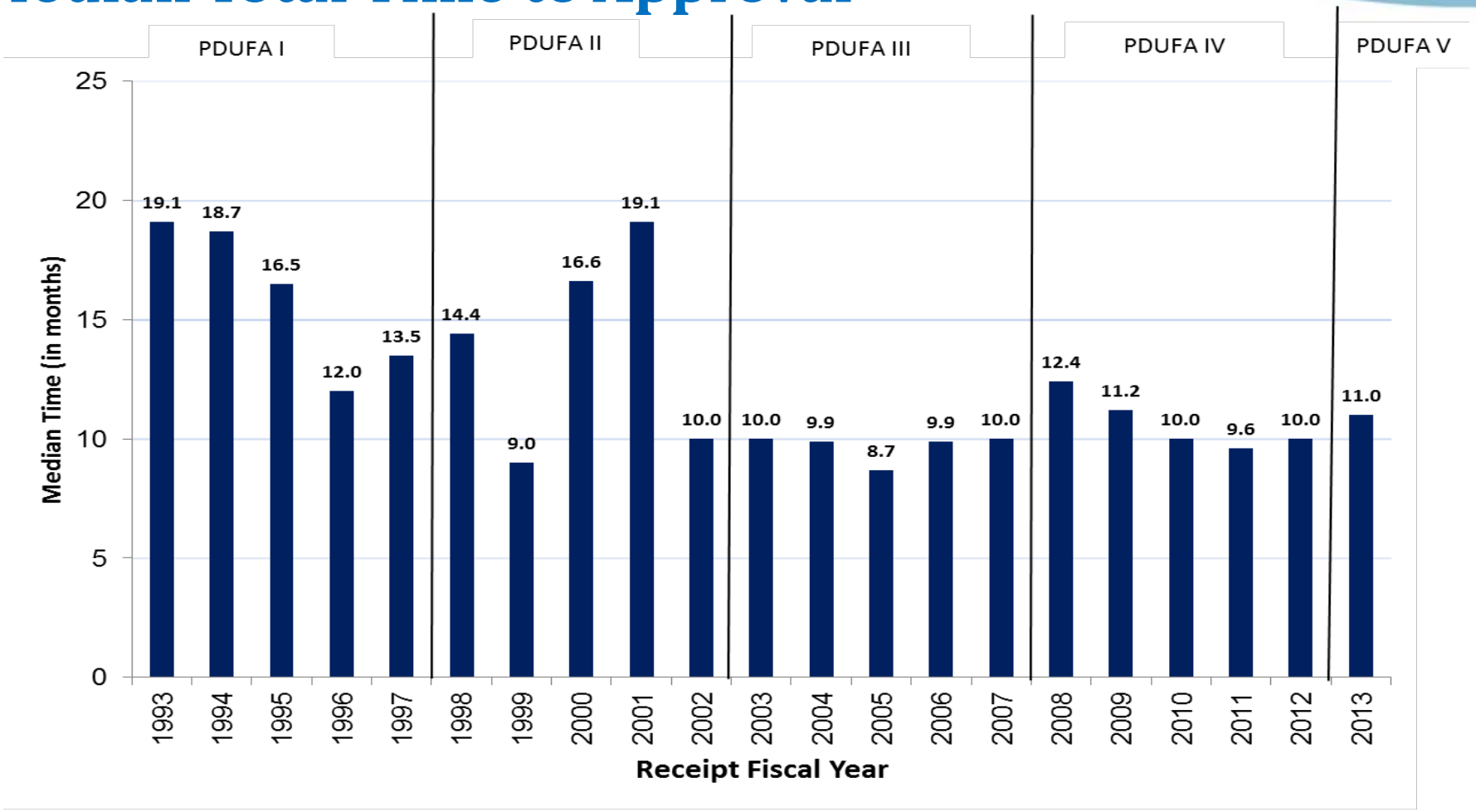
Data as of 12/3/2014

Global New Active Substances First Launches by Region 2001 – 2013



Source: *Scrip Magazine* (2001 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2014)

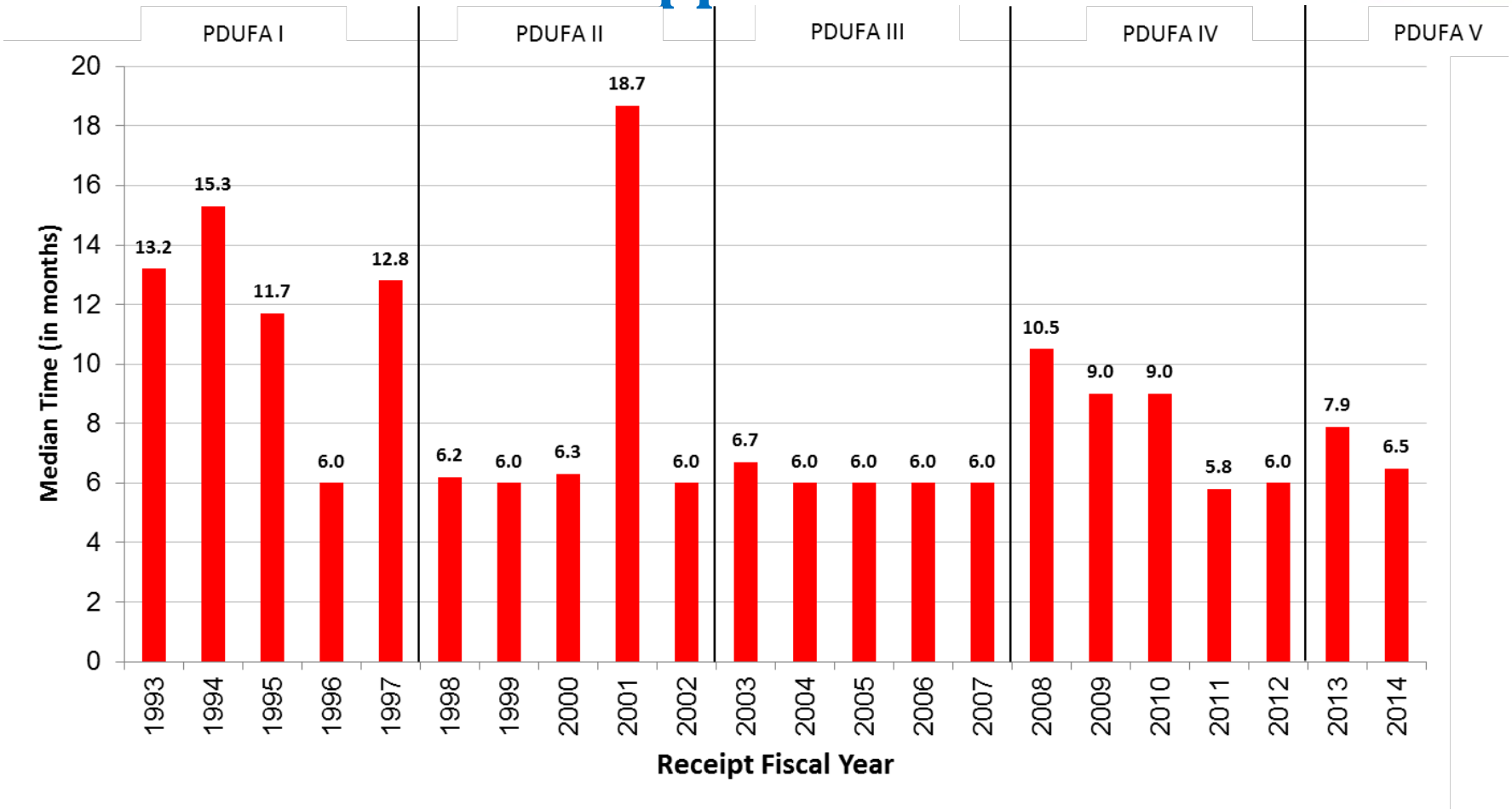
CDER Overall NME NDA/BLAs† Median Total Time to Approval



Data as of 12/3/2014

† Original BLAs that do not contain a new active ingredient are excluded.

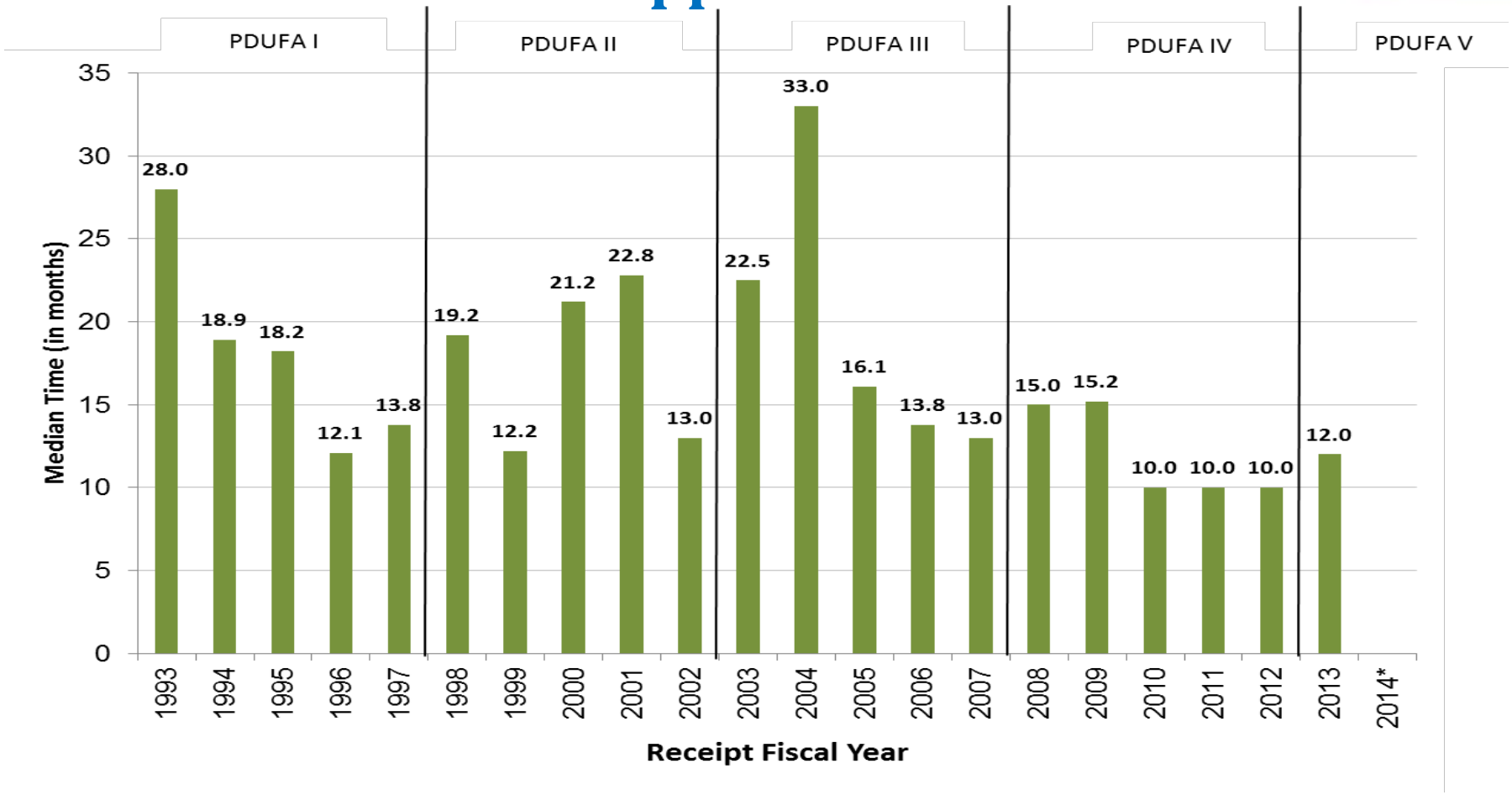
CDER Priority NME NDAs/BLAs† Median Total Time to Approval



Data as of 12/3/2014

† Original BLAs that do not contain a new active ingredient are excluded.

CDER Standard NME NDA/BLAs† Median Total Time to Approval



Data as of 12/3/2014

† Original BLAs that do not contain a new active ingredient are excluded.

* There are no FY14 Standard approvals as of 12/3/2014.

Selected PDUFA V/FDASIA Programs That Impact Drug Development and Review

Review "Program" for NME NDAs and Original BLAs

Goal

- "Improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics." (PDUFA V Goals Letter)

Concept

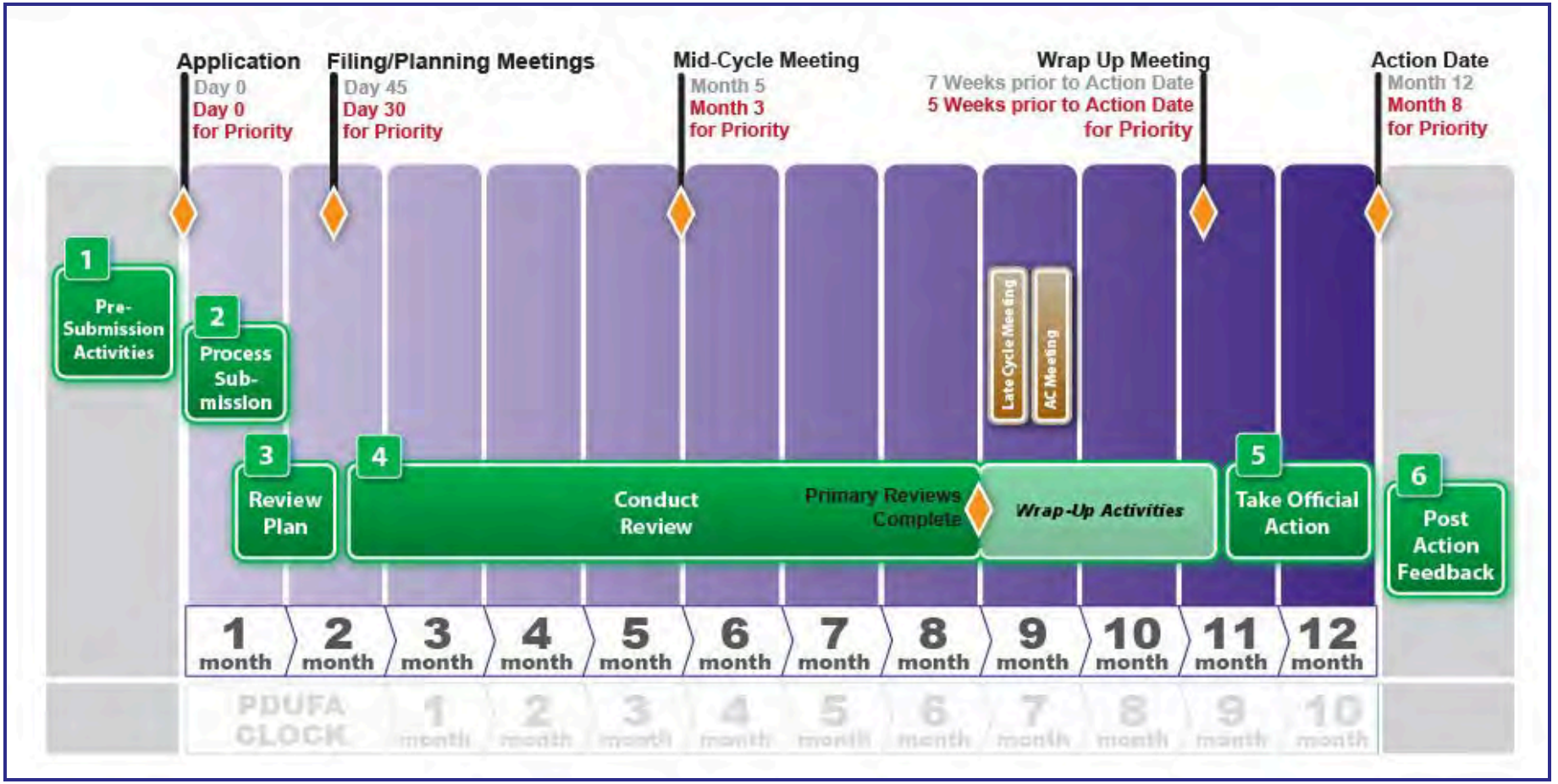
- Better planning before application submission, submission of complete applications, improved communication and transparency between applicant and review team during review, and additional review time will improve the efficiency of the first review cycle, which may decrease the number of additional review cycles prior to approval.

Review "Program" for NME NDAs and Original BLAs

Components

- Pre-submission meeting strongly encouraged
- Complete application at time of submission; incomplete subject to RTF
- 60-day filing review period "off the clock"
- 74-Day Letter
  - Planned review timeline, planned date of internal mid-cycle meeting, preliminary plans on need for AC meeting, early communication of deficiencies/information requests
- Mid-Cycle Communication
  - Within 2 weeks of internal mid-cycle meeting
  - Communication of significant issues identified to date/information requests, preliminary thinking on risk management/REMS, proposed dates for late-cycle meeting, updates on AC plans
- Discipline review letters
  - Summarize preliminary findings/deficiencies by discipline
- Late-cycle meeting (LCM)
  - Focus on information sharing, planning for AC, and planning for the remainder of review

Sample "Program" Review Timeline – Standard Application



Cumulative Activity in the Program

	FY2013 (9/30/13)	Q1 FY2014 (12/31/13)	Q2 FY2014 (3/31/14)	Q3 FY2014 (6/30/14)	Q4 FY2014 (9/30/14)
PSMs	41	51	61	81	93
Receipts	53 33 NDAs 20 BLAs	68 43 NDAs 25 BLAs	78 50 NDAs 28 BLAs	91 60 NDAs 31 BLAs	105 67 NDAs 38 BLAs
RTFs	2	2	2	2	3
Day 74	44	56	70	84	94
MCCs	33	45	58	71	81
DR letters	5	6	6	8	8
Major Amendments[1]	3 3 APs 0 CRs 0 Pending	10 9 APs 1 CRs 0 Pending	14 11 APs 1 CRs 2 Pending	15 11 APs 1 CRs 3 Pending	17 11 APs 1 CRs 5 Pending
LCMs	17	28	42	53	64
FCAs	6 4 APs 0 CRs 2 WDs	23 15 APs 5 CRs 3 WDs	36 23 APs 10 CRs 3 WDs	51 34 APs 13 CRs 4 WDs	64 46 APs 14 CRs 4 WDs
PAIs	6 3 FDA 3 applicant	29 15 FDA 14 applicant	49 28 FDA 21 applicant	78 41 FDA 37 applicant	105 55 FDA 50 applicant

1. Major Amendments are categorized by the quarter in which they were received. The status (AP, CR, Pending) reflects the status of each application as of close of FY2014

AP = Approval
CR = Complete Response
WD = Withdrawal After Filing

PSM = Pre-Submission Meeting
RTF = Refuse to File
MCC = Mid-Cycle Communication
LCM = Late-Cycle Meeting

FCA = First Cycle Action
PAI = Post Action Interview

Note: Because 3 applications were split at action, 48 applications generated 51 actions. Includes CDER as well as CBER data

Program Modifications to Address Learnings

- Mid-cycle communication
  - Intended to be an informal communication between FDA project manager/CDTL and sponsor
  - Meeting has taken on greater importance than anticipated
  - Often involves more attendees from sponsor and FDA
  - Internal FDA guidance modified to encourage providing sponsor with meeting agenda in advance to facilitate improved communication/discussion of preliminary review issues
- Program negotiation in PDUFA V pre-dated Breakthrough
  - Program "timeline" based on full 8 or 12-month review cycle
  - Original construct not well aligned with expedited reviews
  - Modifications of FDA desk reference guide posted on 10/20/14 to accommodate expedited reviews while still honoring Program commitments

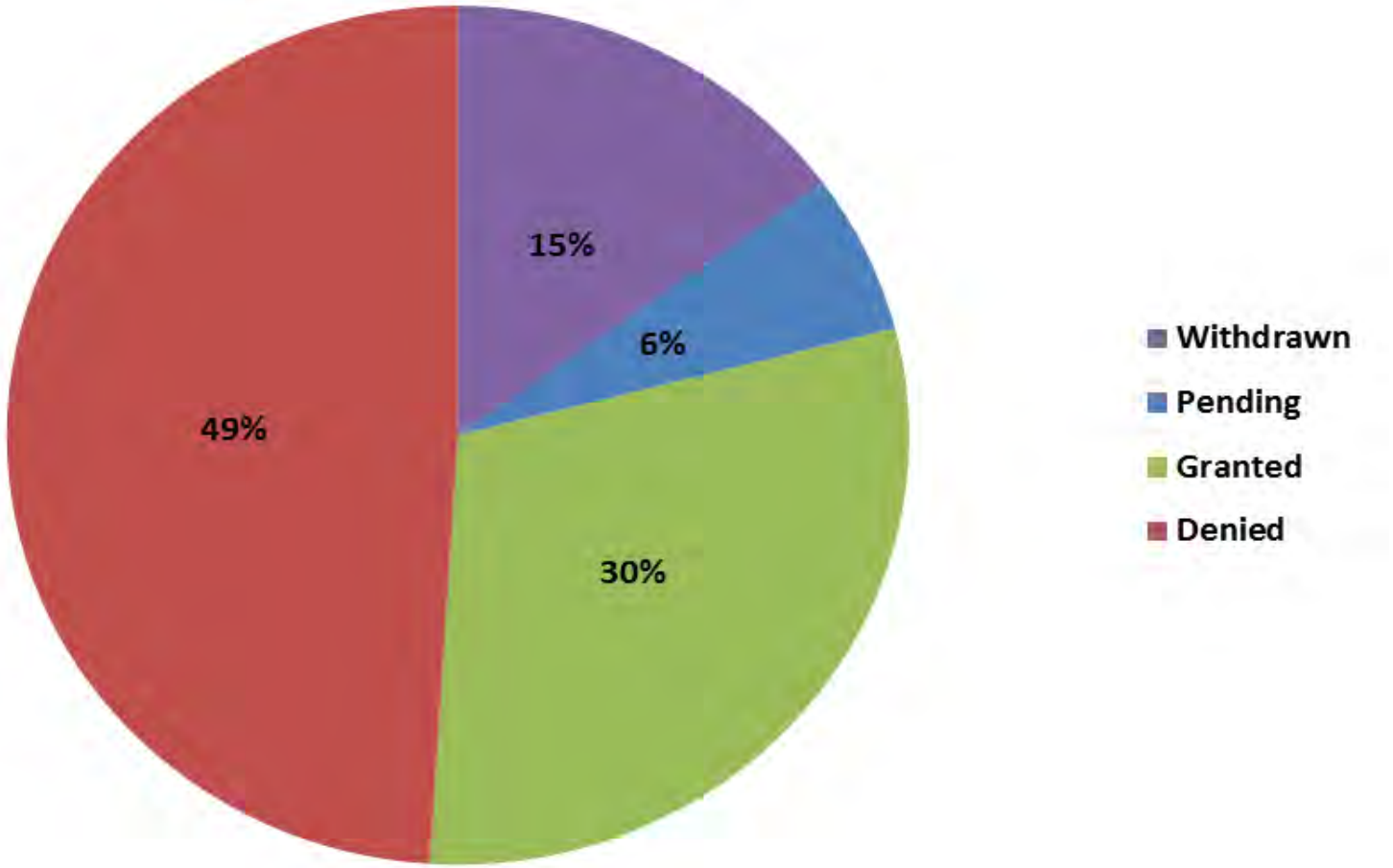
Breakthrough Therapies

- FDASIA program to expedite development and approval of new drugs intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
- FDASIA endorsed and extended FDA's long-standing policy of expediting promising new drugs for serious and life-threatening conditions
- Final guidance "Expedited Programs for Serious Conditions––Drugs and Biologics" issued May 2014

Breakthrough Approvals to Date:

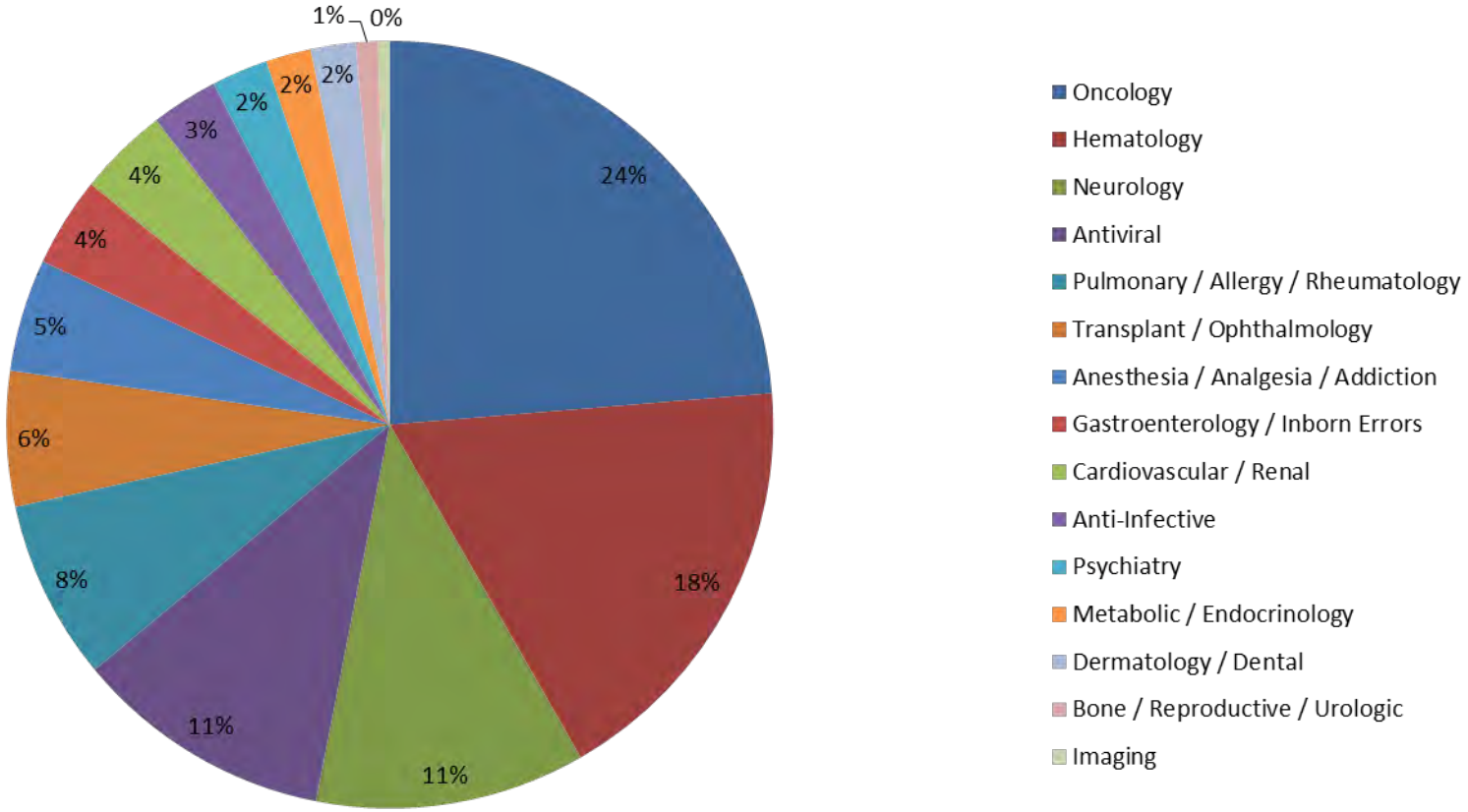
- 2013
  - Gazyva: CLL
  - Imbruvica: Mantle Cell Lymphoma
  - Solvaldi: Chronic Hepatitis C
- 2014
  - Kalydeco, supplement: Cystic Fibrosis
  - Arzerra, supplement: CLL
  - Zykadia: NSCLC, alk+
  - Zydelig: CLL
  - Imbruvica, supplement: CLL
  - Promacta, supplement: aplastic anemia
  - Keytruda: metastatic melanoma
  - Ofev: Idiopathic pulmonary fibrosis
  - Esbriet: Idiopathic pulmonary fibrosis
  - Blincyto: ALL

Current Status of 211 CDER Breakthrough Therapy Requests



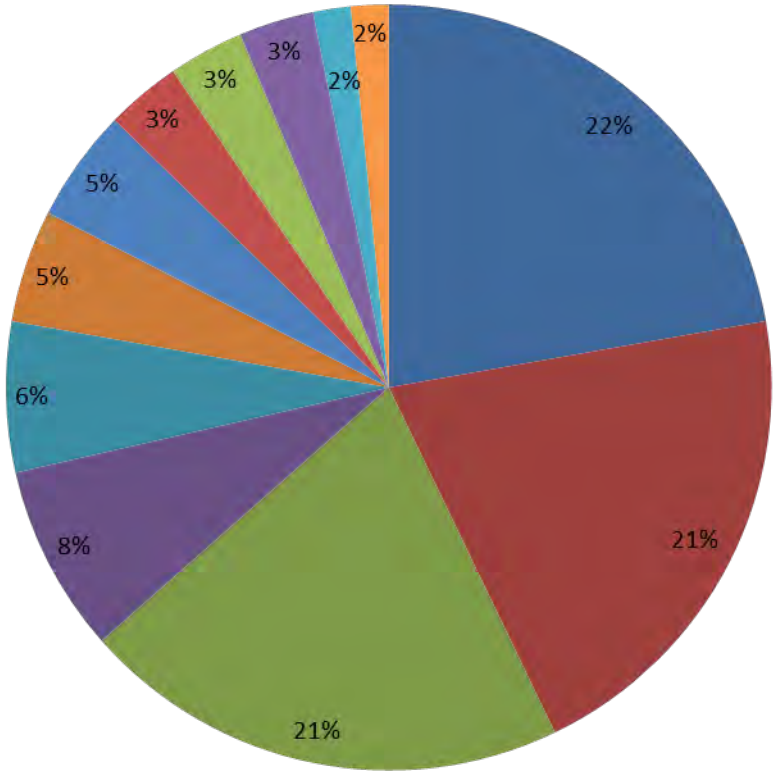
Data as of 11/30/2014

CDER Breakthrough Therapy Requests by Division



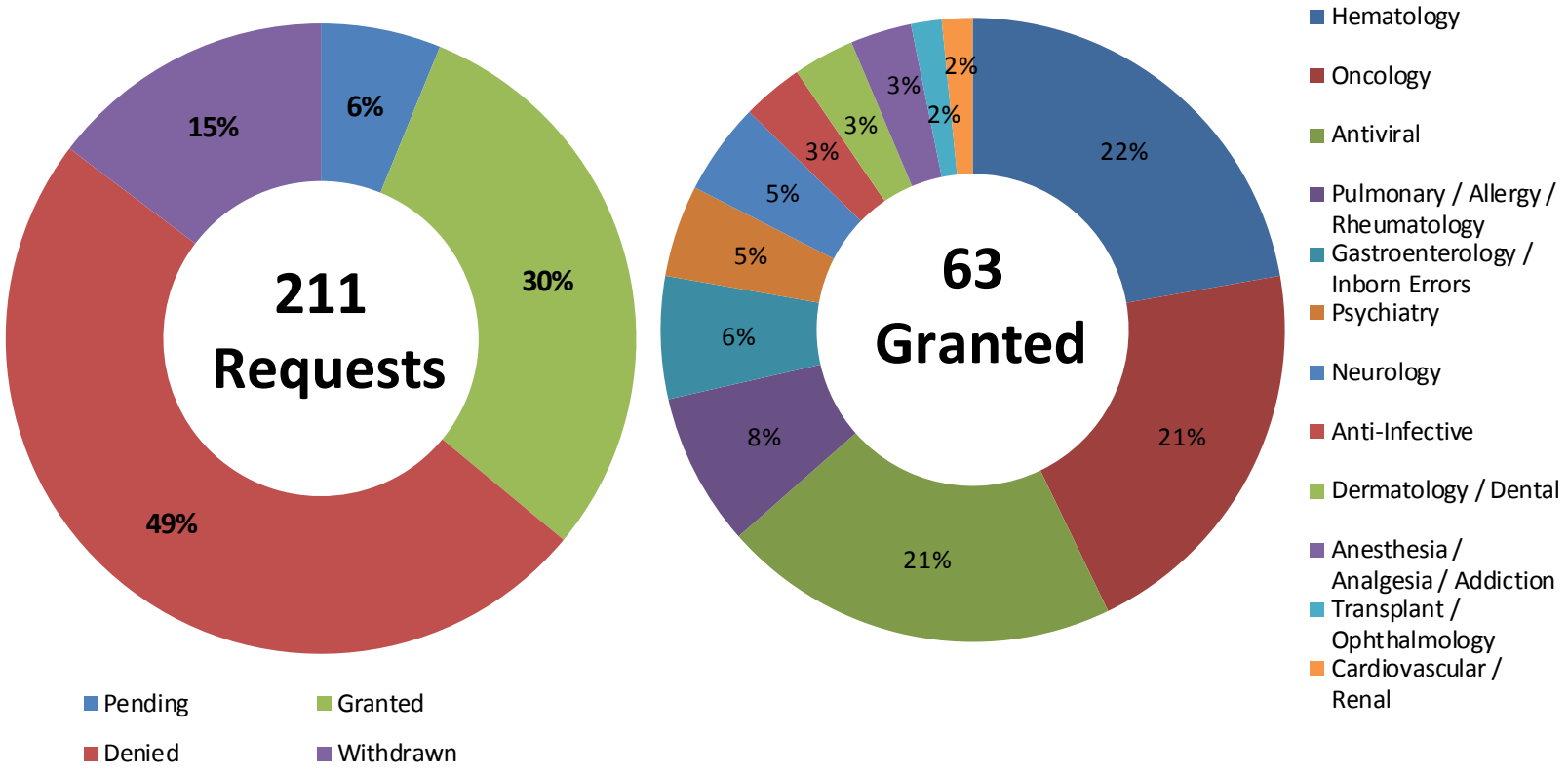
Data as of 11/30/2014

CDER Breakthrough Therapy Requests Granted by Division



Data as of 11/30/2014

CDER Has Granted 63 Breakthrough Therapy Designations Since Inception



Data as of 11/30/2014

Breakthrough Therapies: Two-year Assessment

- "Bar" for approval remains unclear for applicants/public
  - Statutory criteria are subjective, require judgment by FDA
  - BT submission/review under IND impedes clarity/transparency
  - CDER MPC provides consistency for internal decisions
    - 93% initial agreement between review division and MPC
    - Rare disagreements resolved through face-to-face meeting
    - Many reviews now conducted through e-mail
  - FDA working with Brookings on April 2015 workshop on BT designation process
- Pace of requests for BT designation have remained steady
- Clinical development often NOT the rate-limiting step
  - Manufacturing development and scale-up must be accelerated
  - Several examples already of approvals, that while expedited or on time, were delayed due to need to address manufacturing issues

Breakthrough Therapies: Two-year Assessment (2)

- Program commitments are resource intensive for FDA
  - Number of requests and designations have exceeded expectations
  - No resources for BT program were provided under FDASIA
  - We are working to minimize adverse impact on other programs
- Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable; e.g., small numbers of patients treated or inadequate duration of follow up
  - Failure to demonstrate "substantial" improvement over available therapy vs "expected" incremental benefit of development programs
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies

FDA Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary and Assessment		

FDA Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Sets up the clinical context for weighing benefits and risks	
Current Treatment Options		
Benefit	Evaluation of the efficacy and safety data, as well as potential efforts to mitigate risk	
Risk		
Risk Management		
Benefit-Risk Summary and Assessment		

FDA Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition Current Treatment Options Benefit Risk Risk Management	What are the facts and key data? What are the limitations to the evidence?	How should the data be interpreted? What are the implications for the regulatory decision?
Benefit-Risk Summary and Assessment		

FDA Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		

Benefit-Risk Summary and Assessment

A succinct, balanced analysis that clearly explains the regulatory recommendation or action:

- Summarizes conclusions from each decision factor, noting the clinical judgment used in interpreting the evidence
- Includes important differences of opinion among the review team how they were resolved

Benefit-Risk Framework Implementation in CDER

- Significant efforts over the last year to enhance the Clinical Review Template, including integration of the B-R Framework
- Notable features of CRT revision
  - Framework will be part of the Executive Summary
  - New CRT sections on Therapeutic Context and Risk Management that align with the specific Framework dimensions
- Plan to implement revised CRT in early 2015 for NME NDAs and original BLAs
- Revision of remaining memo templates (i.e., CDTL, division director, office director) to include the Framework will follow

Thank You!